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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,855	01/15/2002	Lillian Wei-Ming Chiang	MP100-557P1RM	5102

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MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
CAMBRIDGE, MA 02139

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,855	CHIANG, LILLIAN WEI-MING	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 13, 2006 in response to the Office Action of August 10, 2005, is acknowledged and has been entered. Previously pending claims 24-28 are canceled and 29-32 are amended. Claims 29-33 are currently being examined.

NEW REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to an in vitro method for identifying a compound capable of modulating apoptosis comprising a) combining a test compound with a sample comprising a polypeptide selected from the group consisting of: i) a polypeptide which is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4; and ii) a polypeptide comprising the amino acid sequence of SEQ ID NO:3; under conditions suitable for the polypeptide; b) assaying the ability of the test compound to modulate the glycerophosphoryl phosphodiester phosphodiesterase activity of the polypeptide; c) combining the compound selected in part b) with cells expressing the polypeptide; and d) determining the effect of the compound on apoptosis of the cells; thereby identifying a compound capable of modulating apoptosis (claim 29), wherein the sample comprises the polypeptide or cells expressing the polypeptide (claim 30), wherein the cells are brain cells or neurons (claim 31, 32), wherein the compound is a small molecule, a peptide, or an antibody (claim 33).

The specification discloses that apoptotic cells undergo an orchestrated cascade of events and the various signals that trigger programmed cell death may bring about these events by converging on a cell death pathway that is regulated by the expression of genes that are highly conserved (p. 2, lines 17-22). The specification discloses that SEQ ID NO:3 (encoded by SEQ ID NO:4) is a novel human sequence referred to as NARC16 (p. 8, lines 13-23). The specification discloses a ProDom analysis of NARC16 to indicated that NARC 16 contains a glycerophosphoryl diester phosphodiesterase domain and a glycerophosphoryl diester phosphodiesterase protein T05H10.7-like domain (p. 14, lines 23-26; p. 85, lines 18-30 to p. 86, lines 1-2) wherein a sequence alignment was generated using the Clustal method to recognize that NARC16 protein shares 17.6%, 21.7%, 27.5%, and 22.3% sequence identity with glycerophosphoryl phosphodiester phosphodiesterase of various bacterial species (p. 7, lines 22-30; Fig. 3). The specification discloses that NARC 16 may promote programmed cell death via its glycerophosphoryl phosphodiesterase activity (p. 15, lines 15-16). The specification discloses that glycerophosphoryl phosphodiesterases are involved in the breakdown of phospholipids which eventually produce a glycerol-3-phoshpate product which, in turn, is a substrate for glyceraldehydes-3-phosphate dehydrogenase (GAPDH), of which GADPH has been implicated as a general mediator of programmed cell death (p. 15, lines 17-30 to p. 16, lines 1-2). Finally, the specification discloses that transfection of cells with NARC16 increases programmed cell death compared to negative control cells (Example 2, p. 86-87;Table 1).

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or examples of the putative glycerophosphoryl diester phosphodiesterase domain of SEQ ID NO:3 (NARC16) playing a role in apoptosis nor any compound modulating the putative glycerophosphoryl diester phosphodiesterase activity of SEQ ID NO:3 to modulate apoptosis. The specification provides only low sequence identity to glycerophosphoryl diester phosphodiesterase domains recognized in bacterial species and speculates that the SEQ ID NO:3 comprises glycerophosphoryl diester phosphodiesterase activity that would be modulated to affect apoptosis. However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306).

The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, despite the 17.6%, 21.7%, 27.5%, and 22.3% sequence identity between NARC16's putative domain and the glycerophosphoryl phosphodiester phosphodiesterase of various bacterial species, there is still a range of 82.4% to 72.5% difference and it cannot be predicted, based on

the information in the specification, what affect this difference has on the function of the protein.

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of cellular context on protein function as taught by Bork, with a range of 82.4% to 72.5% dissimilarity to glycerophosphoryl phosphodiester phosphodiesterase bacterial domains, the function of putative glycerophosphoryl phosphodiester phosphodiesterase domain of the SEQ ID NO:3 polypeptide could not be predicted, based on sequence similarity with bacterial glycerophosphoryl phosphodiester phosphodiesterase domains, nor would it be expected to be the same as that of bacterial glycerophosphoryl phosphodiester phosphodiesterase.

As stated above, the specification discloses that apoptotic cells undergo an orchestrated cascade of events and the various signals that trigger programmed cell death may bring about these events by converging on a cell death pathway that is regulated by the expression of genes that are highly conserved. Cavicchio and Jacobson (Poster 5, College of the Holy Cross 7th Annual Undergraduate Summer Research Symposium, 9/8/200, p. 6) teach that NARC16 was found to kill RAT1 cells and an experiment was conducted to find out where in the cell death pathway NACR 16 was initiating apoptosis. Three different inhibitors interfered with the cell death pathway at different points in the cell death pathway and all of the inhibitors inhibited cell death by NARC16 in Rat1 cells, suggesting NARC16 induces death at the beginning of the cell death pathway and functions as an initiator. Given the teachings of the specification and art, it is clear that apoptosis can be modulated at several different points in the cell death pathway, of which NARC16 plays a role in the beginning of the pathway. It is unclear from the specification and art if NARC16 has glycerophosphoryl diester phosphodiesterase activity and if modulation of that activity would modulate apoptosis. Neither the art nor the specification provides a nexus between NARC16 glycerophosphoryl diester phosphodiesterase activity and apoptosis, hence, it could not be predicted that a compound capable of modulating apoptosis could be identified by the claimed method.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839,

166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In view of the novel nature of the invention, the state of the art, what is unknown in the art because of the novel nature of the invention, the lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the claimed invention.

3. All other rejections recited in the Office Action mailed August 10, 2005 are hereby withdrawn.

4. Claims 29-33 are rejected under 35 U.S.C. 112, first paragraph. The closest prior art appears to be Cavicchio and Jacobson (Poster 5, College of the Holy Cross 7th Annual Undergraduate Summer Research Symposium, 9/8/200, p. 6). The art teaches as set forth above but does not teach or suggest a method of identifying a compound capable of modulating apoptosis comprising assaying the ability of the test compound to

modulate the glycerophosphoryl phosphodiester phosphodiesterase activity of SEQ ID NO:3.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER